

Biological Effects of Radiofrequency Fields

Human Health Studies

Epidemiological Studies

Due to ethical and methodological difficulties in studying long term exposure in humans to electromagnetic fields using experimental approaches (Repacholi & Cardis, 1997), observational research is key, *i.e.* epidemiological studies.

The objective of epidemiological studies is to test statistically whether a causal nexus between exposure to an environmental agent and its putative effects on the health status of the exposed subjects can be found. They use specially designed studies that try to determine statistical associations between independent (level of exposure) and dependent variables (health status, development of disease, etc.) by collecting data from population samples. The three most frequently used research designs are cohort, case/control and cross-sectional studies. In relation to RF-based wireless communications, in addition, there are two different exposure situations: to RF in the far field, emitted by base stations, WiFi access points, etc. and to RF in the near field, emitted by handheld devices (*e.g.* mobile phones).

In this section we will review the state of knowledge provided by epidemiological research projects on health risks incurred by exposure to RF fields in several settings, covering the published literature until May 2010. A critical analysis of the methodological issues and summary of current of epidemiological research as well as a short summary of conclusions by expert review groups is presented.

Methodological issues in RF epidemiology

Although epidemiological investigations can be carried out in many areas of environmental health, RF research presents particularly serious methodological challenges. Before going into our literature review, we will briefly discuss them. A more detailed discussion and proposals for solutions will follow the review.

According to the World Health Organization publication on *Electromagnetic Fields, Environmental Health Criteria* series (WHO, 1993),

“epidemiological studies on the association between cancer and adverse reproductive outcomes and RF fields are made difficult by a number of factors: most members of any population are exposed to levels of RF that are orders of magnitude below thermally significant levels, it is very difficult to establish RF exposure in individuals over a meaningful period of time, and control of major

confounders is very difficult.”

Despite having been written in 1993 our opinion is that this statement is still valid. Clinical epidemiology has evolved a lot since that date. However, it has been unable to solve many of the fundamental methodological problems which are inherent to the problem's nature, as we shall see later on.

The detection of associations (or cause-effects relationships) in epidemiological research which investigates low-level environmental agents should allow for sufficient latency, sufficient range of exposure, including high exposure, and ability to accurately classify individuals into several exposure groups.

In this regard the main limitation of these epidemiological studies is that they are only able to show associations between dependent and independent variables, and usually do not have enough power, because they were observational studies with many uncontrolled variables, to establish definitive cause-effect relationships as it happens with the experimental approaches, but may only inform whether causality is probable. Several sources of bias and confounding factors make it difficult to draw conclusions with scientific evidence of greater strength, as noted by Bradford Hill, who listed nine points that must be satisfied in an epidemiological study.

Despite these difficulties, its high costs and long duration, epidemiological studies are crucial for proper risk assessment. The active database of registered scientific papers of the Electromagnetic Fields and Health Group of the World Health Organization (WHO-EMF) listed until the first quarter of 2010 about 383 published epidemiological studies, of which 147 dealt with mobile telephony and wireless data communication. Of these, 65 were case/control and 15 were cohort studies, comprising about 50% of published papers. Thirty two epidemiological studies investigated the association between RF exposure in this sub-area with subjective symptoms (21), nervous system and behavior (8), and teratogenicity, reproduction and development (3).

Ecological Studies: The Extent of EMF Irradiation

Epidemiological studies, since they are carried out in natural settings, must take into account the degree of exposure to all sources of radiofrequency, both natural and artificial, and the contribution of each frequency. Until recently, very little was known about the average exposure of human beings in urban environments to artificial radiofrequency fields used in telecommunications, particularly mobile telecommunications, in terms of its signal strength and power density distribution.

One study, by Frei *et al* (2009) used personal dosimeters worn continuously by Swiss volunteers during one week to evaluate the degree of exposure. They discovered that the mean exposure was low (0.13 mW/m² ranging from 0.014 to 0.881 mW/m²). This mean level corresponds to a field gradient of 0.22 V/m, well below the safety limits of 10 V/m). Exposure to frequencies used in mobile telecommunications was mainly due to cell phone base stations (32%) and handsets (29%), and DECT cordless phones (22%). The highest exposures were recorded inside closed transportation vehicles such as trains (1.16 mW/m²) and tramways or buses (0.36 mW/m²) and airports (0.74 mW/m²), and were on average double in daytime than in nighttime (0.08 mW/m² only).

Besides mobile voice communication, recent concern has been expressed on the degree of daily exposure to wireless data communication devices, such as WLAN (Wireless Local

Area Networks) and Bluetooth. Other common sources of RF exposure have been little investigated are baby surveillance devices (electronic babysitters), domestic cordless telephones and wireless headphones for indoor usage. Schmid *et al.* (2007a) have measured combined exposures for all these indoor devices in homes and offices, arriving at the conclusion that they are low, the average being approximately 0.1% of the ICNIRP power density level safety limit. WLAN exposures were in the order of 20 mW/m². None of the devices, even those near the body, exceeded these limits. Outdoor measurements of LAN wireless base stations resulted 2 or 3 orders of magnitude lower than indoor levels, resulting negligible in relation to safety levels.

Joseph *et al.* (2008) estimated SARs (Specific Absorption Rates) for outdoor exposure of the general public for several locations and scenarios. The average level of GSM base stations was 0.26 V/m, generating a 95th percentile SAR of 2.08 µW/kg (the ICNIRP recommended safety level being 4 W/kg for the whole body). In other words, observed SAR is approximately 5 tenths of a million times less than the safety level.

Information Sources for the Review

Two main databases were used for finding the sources of information used in the present review: MEDLINE (US National Library of Medicine, searched on-line via PubMed), and the database of papers maintained by the WHO-EMF Project. We complemented the search with news alerts from various news services, such as RF Gateway.

We consulted also the main comparative surveys of the literature, critical reviews and meta-analyses in order to better filter the large number of papers as to relevance: Breckenkamp *et al.* (2003), Rösli *et al.* (2003), Kundi *et al.* (2004), Elwood (2004), Lahkola *et al.* (2006), Krewski *et al.* (2007), Moulder *et al.* (2005), Hardell *et al.*, (2007), Ahlbom *et al.* (2004, 2009) Important methodological issues in regard to large scale epidemiological studies of exposure to radiofrequency (RF) have been posed by Rothman *et al.* (1996), Schüz & Mann (2000), Ahlbom *et al.* (2004), Morrissey (2007), Neitzke (2007), Kuhnlein *et al.* (2008), which we have used for the present review.

Two reviews by Ahlbom *et al.* (2004, 2009) examined the published literature on epidemiology of the effects of RF from 100 kHz to 300 GHz on human health, dividing it into studies of RF exposure from occupational sources, from transmitters, and from mobile phones; and covering possible effects of long-term exposure on the risk of diseases, such as cancer, heart disease, and adverse outcomes of fertility and pregnancy. These reviews were important because they were commissioned by ICNIRP and carried out by its group of experts in epidemiology.

In addition, we have studied closely and taken into account the expertise of international and national committees that have carried out extensive reviews of the literature, such as ICNIRP, the Independent Expert Group for Mobile Phones (IEGMP), the former United Kingdom Radiological Protection Board (now Health Protection Agency), and others. For example, an expert group from the European Commission called SCENIHR (Scientific Committee on Emerging and Newly Identified Health Risks), has produced an opinion on the "*Possible Effects of Electromagnetic Fields (EMF), Radio Frequency Fields (RF) and Microwave Radiation on Human Health*", which updates that provided by CSTEE (Scientific Committee on Toxicity, Ecotoxicity, and the Environment) in 2001; both evaluations were based primarily on peer-reviewed articles. Recent board reviews by the

Swedish Radiation Safety Authority (SSM, 2009) were especially considered for the present literature review.

Cancer Incidence and Mortality

Community Exposure Studies

This is the category of epidemiological study that lacks good quality data. Small, low quality studies, published in non-peer reviewed journals, or as technical reports or conference abstracts, and which lacked proper controls and significant number of subjects, were excluded from the present review, since the quality of evidence they provide is very low.

Of the eight epidemiological studies on cancer mortality and incidence, published on exposure on the general population until 2001, as examined by Ahlbom *et al* (2004), all of them focused on the possible effect of radio and TV transmitters on brain tumors and childhood leukemia. All had a small number of cases and typically involved less than five observed cases of cancer. Distance from the source antenna was the main criterion of classification of exposure, which is quite an inadequate way of quantifying exposure. Risk ratios were small, near unity, so that no association between proximity to an antenna and cancer incidence or mortality could be demonstrated. The assessment by Ahlbom *et al* (2004) clearly states:

“To date no acceptable study on any outcome has been published on this. On the one hand, results from valid studies would be of value in relation to a social concern; on the other hand, it would be difficult to design and conduct a valid study, and there is no scientific point in conducting an invalid one.”

This situation has not changed until the date of the present review and no new significant community exposure studies has contributed to the scientific knowledge. For recent studies in children see section below.

More robust and extensive studies are clearly needed in this area. A group of experts has recently analyzed the feasibility of such studies (Neubauer *et al*, 2007), by examining the critical methodological issues, and concluding that they are feasible, but the exposure contributions from all relevant radio frequency sources would have to be taken into account, not only those used in mobile telephony, for instance. Most epidemiological studies don't do this, and are somewhat irrational in assuming that the only source of RF which is present in the environment is the one that they are focusing on, and that the other sources were distributed evenly across all comparison groups (cases and controls). Since many of these studies are retrospective, they are unable to get information on exposure, therefore they are not valid.

Although all this is very well known, epidemiological investigators seem reluctant to pursue them, due to several reasons, the main ones being that proper and reliable instruments, capable of measuring continuously personal exposure have only recently been developed. Schüz *et al* (2000) have demonstrated that

“studies at the population level on suggested adverse effects of radio waves from mobile phone base stations are not feasible since no valid metric for estimating historical exposures is currently available. The pace of radio infrastructure

development is also such that today's measurements are unlikely to be good proxies for either past or future exposures. The complex propagation characteristics affecting the beams from base station antennas include shielding effects and multiple reflections from house walls and other buildings. These factors, combined with the presence of other environmental sources of radio waves, cause distance from a base station to be a poor proxy for exposure to radio waves indoors."

Furthermore, field power densities of typical antennas are very low so that a biophysical effect is highly unlikely to occur (Repacholi, 1998). Thus, investigators have concentrated on epidemiological studies of cell phone and other users of RF devices.

Studies with Users of Cell Phones

Ahlbom *et al.* (2004) examined 10 epidemiological studies related to cancer carried out between 1999 and 2003, being three in Sweden (all from the same authors, led by L. Hardell), one in Finland, one in Denmark, and the rest in the USA. Only those studies with well-defined exposure groups, for a sufficient time span (at least 2 to 3 years) were included. Lakhola *et al.* (2006) performed a meta-analysis of 12 original epidemiological papers reporting on brain tumor incidence with a total of 2,780 cases, the majority of the reviewed studies overlapping with those by Ahlbom, but they improved on the statistical methodology, by carrying out a meta-analysis, recalculating odds ratios (OR) for better precision and pooling results for the same kinds of histological tumors.

Kundi *et al.* (2004) reviewed almost exactly the same set of epidemiological studies reviewed by Ahlbom (2004) and Lakhola (2006), but came to different conclusions. Ahlbom *et al.* (2009) reviewed more recent epidemiological studies, including most of the joint INTERPHONE studies published by 2009 (which we will discuss in more detail in a specific section, below).

Except from two cohort studies, all the other studies used the case-control methodology. The number of cases studied were larger than those for community exposure to transmitters. Outcomes studied were mainly tumors of the CNS and eye, such as high-grade and low-grade glioma, acoustic neuroma, uveal melanoma and meningioma. The rationale for this is that modeling studies have shown larger absorption and distribution of RF energy from cell phones around the head and neck regions, at least for those who do not use a hands-free device. One study covered tumors of the salivary glands, and five analyzed tumors of all kinds. Fourteen independent calculations of risk ratios (RR) were below or equal to 1, meaning that no risk was found for cell phone users for those studies. Five studies had RR slightly larger than 1 (between 1.1 and 1.5), but these were also non-significant differences.

One study by Hardell *et al.* (2003) had a significant RR of 3.5 for acoustic neuroma incidence in patients using analog cell phones, and reporting at the same time a laterality effect (incidence of tumor was higher for the side of the head reported to be the dominant one by cell phone users). This last study made headlines all over the world, despite the fact the nine other showed no associations. According to an analysis on laterality of effects carried out by the SCENIHR EMF Health Group and published in a report in 2009, this parameter is highly susceptible to reporting bias as cases know which side of their head is affected by the tumor, whereas controls do not know which side of their head will be relevant for analyses (in a matched study, it is the side of the head where the tumor occurred in their corresponding matched case). Therefore overreporting of the affected

side of the head among cases may occur. Posteriorly, the study by Hardell et al. (2007) was refuted by other authors, due to some methodological issues, such as a lack of control for important confounding factors, and because other groups which had analysed the risks for the same tumor were unable to reproduce their results in the same region of Europe (Scandinavia).

With the exception of acoustic neuromas, all other papers of case/control studies reviewed by Ahlbom *et al.* (2004) presented absence of association between the use of cell phones and tumors of the parotid gland, uveal melanoma and leukemia. Two earlier case-control studies with a smaller data set in Denmark had demonstrated no evidence of increased risks for cell phone users in regard to the incidence of acoustic neuromas (Christensen *et al.*, 2004), meningioma and low- and high grade glioma, even for users with more than 10 years of continuous use (Christensen *et al.*, 2005).

Longitudinal Studies

The two only retrospective methodologically sound cohort studies were carried out in the USA and in Denmark.

The first large cohort study, (Dreyer *et al.*, 1999, Rothman *et al.* 1996) analyzed 1-year follow-up of mortality in a cohort of 285,561 non-corporate users of mobile phones in the USA, with no evidence of general mortality (RR of 0,86). This study is not meaningful as the latency is not sufficient for any mortality outcome. It was the first study to demonstrate that the overall mortality of the cohort was less than in the general population, a finding that was confirmed by other studies with specific causes of mortality, such as cancer. If this finding were to be interpreted in the light of what relative risk means, one would have to assign a “protective” or “risk decreasing” characteristic to the fact of using a cell phone. Of course this is hard to believe, most probably it is due to the a confounding variable, such as those that the Danish cohort study was able to demonstrate, like a better income, with corresponding better general health, a higher level of education, with corresponding awareness about health, better prevention, etc. occurring more among cell phone users than in non-users.

This should serve as a lesson to those epidemiologists who accept this explanation for RRs smaller than unity, but tend to assign “high” risk to cell phones when the RR lies above unity, at the same level of variation.

The second large cohort study, by Johansen *et al.* (2001), was the first nationwide cancer incidence study of cellular phone subscribers that examined records up to 15 years of usage, and reported an overall Standardized Incidence Ratio (SIR) of 0.89 (within a very narrow 95% confidence interval of 0.86 to 0.92) for all types of cancer. SIRs are calculated by dividing the number of observed cancer cases in the cohort by the number expected in the population. Overall, 3391 cancers were observed with 3,825 expected by chance. The apparent protective effect of using cell phones was interpreted by the authors, with basis on more detailed analysis, as a decrease of lung cancers possibly associated with a larger reduction in smoking among older subjects.

The same group (Johansen *et al.*, 2002b) published an expanded sample of the same study, including 420,095 private cellular network subscribers (80% of all subscribers in the country). They compared cancer incidence rates in phone users with national rates, according to gender, age, and period. Of the 15,000 cases of cancer expected by chance, some 14,250 were observed. The epidemiological study showed no relation to risk of brain

and nervous system cancers [SIR 0.95], in relation to age at, or time since, first subscription, phone type, or tumor location. The Danish study was recently updated with follow ups of cell phone subscribers reaching back up to 21 years (Schüz *et al.*, 2007), with the first cellular telephone subscription between 1982 and 1995 and who were followed through 2002 for cancer incidence of all types of tumors. Cellular telephone use was not associated with increased risk for brain tumors (SIR = 0.97), including gliomas (SIR = 1.01) and meningiomas (SIR = 0.86) acoustic neuromas (SIR = 0.73), salivary gland tumors (SIR = 0.77), eye tumors (SIR = 0.96), or leukemias (SIR = 1.00). Among long-term subscribers of 10 years or more (more than 56,000), cellular telephone use was not associated with increased risk for brain tumors (SIR = 0.66, showing a strong protective effect), and there was no trend with time since first subscription. Since a cause-effect relationship in this case is highly improbable, *i.e.*, using cell phones per se would not be expected to increase good health, the observed reduction in relative risk below 1 could be attributed to confounding variables, such as: long term users started to use cell phones when they were very expensive, so a higher income was required (Rothman *et al.*, 1996). People with higher income are known to have better general health, take preventive care of themselves and go more often to physicians and hospitals than younger and less affluent people (although these differences are less relevant for highly developed countries such as Denmark and Sweden). The authors reported that *“no evidence was found for an association between tumor risk and cellular telephone use among either short-term or long-term users. Moreover, the narrow confidence intervals provide evidence that any large association of risk of cancer and cellular telephone use can be excluded.”*

The Danish study had some peculiarities. It was carried out entirely by doing record linking analysis, which has been possible only due to the excellence and completeness of population records (cell phone subscriber, National Population Registry and the National Cancer Registry), using a nationwide ID number.. Second, the cohort was very large and extensive in time, as well as comprehensive (80% of all Danish cell phone subscribers). There was no assessment of degree of exposure, frequency of use, use of hands-free, etc, and there was no way of ascertaining for sure whether subscribers actually corresponded to users. Although a later investigation by Punch *et al.* (1996) was able to demonstrate that there is a relatively high correlation for that (about 75%). Corporate user subscriptions (a large number, more than 200,000) were not included in the study, which might be a potential source of selection bias.

Except for acoustic neuromas, all the other studies reviewed by Ahlbom *et al.* (2004) showed no association between cell phone use and parotid gland tumors, uveal melanoma, meningiomas and leukemias.

Interestingly enough Kundi *et al.* (2005), reviewing almost exactly the 9-10 studies reviewed by Ahlbom (2004) and Lakhola *et al.* (2005), arrived at the opposite conclusion, *i.e.*, that *“all studies approaching reasonable latencies found an increased cancer risk associated with mobile phone use. Estimates of relative risk in these studies vary between 1.3 and 4.6 with highest overall risk for acoustic neuroma (3.5) and uveal melanoma (4.2), and there is evidence for enhanced cancer risk with increasing latency and duration of mobile phone use.”* The results are largely based on a studies of a single research group, headed by Hardell in Sweden, which are not consistent with the other 6 studies from other groups.

Another review published by Valberg *et al.* (2007) on scientific evidence about exposures and health consequences of base stations and wireless networks arrived at the same

conclusions as Ahlbom *et al* (2004).

The most important and recent set of systematic epidemiological studies, however, was the INTERPHONE Project, which deserves a separate discussion, as follows.

A review of the INTERPHONE studies

Beginning in 2001, a series of ambitious, well designed, large case-control epidemiological studies coordinated and partly financed by the International Agency for Research on Cancer (IARC) were started in 13 countries (Australia, Canada, Denmark, Finland, France, Germany, Israel, Italy, Japan, New Zealand, Norway, Sweden, and the United Kingdom) using a common protocol, in order to allow for a pooled analysis of all national data. Named INTERPHONE, this international effort started publishing preliminary data in 2004, and in 2007 the first paper describing methods appeared in print (Cardis *et al*, 2007). The first complete publication reporting the pooled results for two types of brain tumors, glioma and meningioma, was published in May 2010, after a protracted period (The INTERPHONE Research Group, 2010). The final publication for two other types of tumors, acoustic neuroma and tumors of the salivary gland, was still pending at the time of submission for publication of this review.

The INTERPHONE study focused on tumors in locations most likely to be affected from higher exposure to RF fields during mobile phones use: it included 2,765 cases of glioma, 2,425 of meningioma, 1,121 of acoustic neuroma, 109 of malignant parotid gland tumor and 7,658 controls). Detailed information about the history of mobile phone use, and a number of known and potential risk factors were collected by means of an in-person computer assisted interview (CAPI) conducted by a trained interviewer. Most significant is the fact that for the first time, several preparatory validation studies and refined epidemiological and statistical techniques were used in order to understand better and to decrease the influence of biases and confounding variables which operated in previous case-control studies. The INTERPHONE studies have been eagerly awaited by the scientific community, as well by health authorities and the mass media, and ICNIRP, WHO and other agencies have postponed their official statements about RF and health in expectation of these results, based on its design characteristics and size. We review them here briefly.

One of the first INTERPHONE studies examining the incidence of acoustic neuromas (Shoemaker *et al*, 2005) used a pooled set of 6 separate case control studies carried out in Nordic Europe and UK under the common protocol. It found that the risk of this tumor in relation to regular mobile phone use in the pooled data set was not raised (OR = 0.9), and that there was no association of risk with duration of use, lifetime cumulative hours of use or number of calls, for phone use overall or for analogue or digital phones separately. They found however, a small elevated risk of a tumor on the same side of the head for use for 10 years or longer (OR = 1.8). The study suggested that there is no substantial risk of acoustic neuromas in the first decade after starting mobile phone use. The Japanese INTERPHONE branch of the same study reported essentially the same results (Takebayashi *et al*, 2006). The French INTERPHONE study (Hours *et al*, 2007) also reported no significant increased risk for glioma, meningioma or neuroma, although glioma patients had a slightly positive, non significant OR among heavy users. The UK part of the study of gliomas had completely negative results, ascribing a higher but non-significant ipsilateral risk to recall bias (Hepworth, 2007). The result confirming no association of glioma and meningioma incidences to cell phone exposure under 10 years was confirmed

by a Nordic INTERPHONE study in 5 countries (Lakhola *et al*, 2008).

Lönn *et al* (2005) in Sweden, did a case-control study of 644 brain glioma and meningioma cases and 674 controls, and concluded that for regular cell phone use, the odds ratio were 0.8 for glioma and 0.7 for meningioma, with similar results for more than 10 years of mobile phone use. Likewise, no risk increase was found for ipsilateral phone use for tumors located in the temporal and parietal lobes, type of tumor histology, type of phone and intensity of use. This study included a large number of long-term mobile phone users, and the authors conclude that the data do not support the hypothesis that mobile phone use is related to an increased risk of glioma or meningioma, thus being the first one to directly contradict the publications of their countryman L. Hardell.

Another INTERPHONE study was completed and published in 2008, which analyzed the risk of parotid gland tumors in cell phone users in Israel (Sadetzki *et al*, 2008a). Lönn *et al* (2006) had previously reviewed the epidemiological evidence on salivary glands cancer and cell phone use in Denmark and had concluded that the data did not support such an association (for regular mobile phone use, regardless of duration, the risk estimates for malignant and benign tumors were 0.7 (95% confidence interval: 0.4, 1.3) and 0.9 (95% confidence interval: 0.5, 1.5), respectively. Similar results were found for more than 10 years' duration of mobile phone use. The Sadetzki study, however, found an elevated risk of ipsilateral benign and malignant tumors (ORs in the highest category of cumulative number of calls and call time without use of hands-free devices were 1.58 (95% confidence interval: 1.11, 2.24) and 1.49 (95% confidence interval: 1.05, 2.13), respectively), provoking a lot of controversy and misleading statements in the press. Parotid cancer is very rare (2-3 cases per million). Carcinogenesis induced by long term smoking has been suggested as a risk factor for some head and neck tumors (Marur & Forastiere, 2008), including parotid cancer (Sadetzki *et al*, 2008b).

The final publication of INTERPHONE pooled results for glioma and meningioma case/control studies in 13 countries (The INTERPHONE Research Group, 2010), arrived at the conclusions that a below-unity odds ratio (OR) was obtained for glioma [OR 0.81; 95% confidence interval (CI) 0.70-0.94] and meningioma (OR 0.79; 95% CI 0.68-0.91), in relation to being a regular phone user anytime. The authors interpreted this OR as possibly reflecting participation bias or other methodological limitations and not of real protective effect. No increased OR was observed 10 years after first phone use (glioma: OR 0.98; 95% CI 0.76-1.26; meningioma: OR 0.83; 95% CI 0.61-1.14). ORs were below one for all deciles of lifetime number of phone calls and nine deciles of cumulative call time. In the tenth [highest] decile of recalled cumulative call time, the OR was 1.40 (95% CI 1.03-1.89) for glioma, and 1.15 (95% CI 0.81-1.62) for meningioma. However, the authors noted highly implausible values of reported phone use in this group, such as 12 hours of use per day, potentially biasing the results and rendering them artificially high. Regarding location of the tumor, ORs for glioma tended to be greater in the temporal lobe than in other lobes of the brain, which corresponds to the part of the brain more exposed to the cell phone RF radiation, but the confidence intervals for lobe-specific estimates were wide. ORs for glioma tended to be greater in subjects who reported "usual" phone use on the same side of the head where their tumor was located, than on the opposite side, but on basis of the methodological studies already cited above, this results might be explained by a recall bias, since diseased individuals tended to assign their preferred mobile phone use side of the head to the one they sustained the tumor.

Another key finding of the INTERPHONE study was that it did not matter whether the person was an analogue or digital cell phone user the study found no increased risk of brain tumours.

The WHO has published soon after a fact sheet on EMF and health (WHO, 2010), stating about the INTERPHONE final publication:

'A retrospective case-control study on adults, INTERPHONE, coordinated by the International Agency for Research on Cancer (IARC), was designed to determine whether there are links between use of mobile phones and head and neck cancers in adults. The international pooled analysis of data gathered from 13 participating countries found no increased risk of glioma or meningioma with mobile phone use of more than 10 years. There are some indications of an increased risk of glioma for those who reported the highest 10% of cumulative hours of cell phone use, although there was no consistent trend of increasing risk with greater duration of use. Researchers concluded that biases and errors limit the strength of these conclusions and prevent a causal interpretation.'

The results of INTERPHONE have been challenged by some science advocacy groups, such as BIOINITIATIVE, and by some epidemiologists, as having a number of significant methodological flaws (Sarrachi and Samet, 2010), including selection, recall biases, exclusion of young adults and children, and of brain tumor cases because of death and illness, all of which might lead to artificially low ORs. The critics have also called attention to INTERPHONE's failed definition of regular user (a regular user was defined as one call per week for at least 6 months, an exposure so low that might severely under-estimate risk in the exposed population).

Although many comments on the May 18, 2010 publication emphasized the inconclusiveness of the study, we don't think this conclusion are entirely warranted. In fact, INTERPHONE is the largest and most carefully controlled case control, with the largest number of long-term cell phone users on brain and head tumors. Odds ratio were universally low, hovering around unity,. The INTERPHONE results are in agreement with most other *in vitro* and *in vivo* studies, as well as with other case-control and large register-based cohort studies with more than 400,000 participants.

Therefore, overall conclusions by highly respected institutions, such as ICNIRP, reflected the positioning of the scientific community:

ICNIRP (<http://www.icnirp.de/documents/ICNIRPnote.pdf>).

"Overall, the study did not find an increase in the risks of glioma or meningioma in relation to mobile phone use. " ... "ICNIRP agrees that the biases and errors in the study precluded a causal interpretation of the results."

WHO (<http://www.who.int/mediacentre/factsheets/fs193/en/index.html>), in their respective statements published in 2009 and 2010, that there is no evidence for detrimental health effects on human beings by low-power radiofrequency devices used for mobile communications, are amply justified, despite contrary positions by a few groups and individuals.

In addition the US Food and Drug Administration (FDA) (<http://www.fda.gov/downloads/ForConsumers/ConsumerUpdates/UCM212306.pdf>) has

stated that

“The recent Interphone findings, posted online in the June 2010 International Journal of Epidemiology, did not show an increased risk of brain cancer from using cell phones. Although some of the data suggested an increased risk for people with the heaviest use of cell phones, the study’s authors determined that biases and errors limit the strength of conclusions that can be drawn from it. According to WHO, cell phone use has become much more prevalent and it is not unusual for young people to use cell phones for an hour or more a day. This increasing use is tempered, however, by the lower emissions, on average, from newer technology phones, and the increasing use of texting and hands-free operations that keep the phone away from the head.”

It is important to note, however, that no epidemiological studies with long term exposures larger than 15 years have been published so far. Considering that even very aggressive environmental agents, such as UV radiation by solar exposure, display proven latencies of 20 years or more, the state of knowledge of RF exposure has a large gap here. It may be the case that effective latencies for cancer causation may exceed the average lifetimes of people who are currently adults, but might be relevant for users who are children or young today. Unfortunately, there are still no large epidemiological study for this age bracket, despite that children, adolescents and young adults constitute a larger, and increasing part of heavy users of cell phones, PDAs and notebook computers with wireless data access.

Systematic reviews based on meta-analysis

An important technique for the systematic review of the literature is meta-analysis, which uses special statistical methods to combine and to compare different studies with a common outcome and similar research design. The selection criteria for studies that compose the meta-analysis is an important consideration because to any statistical analysis biases can be introduced by this selection and influence the results. In addition, sometimes it is difficult to draw conclusions from meta-analysis due to the heterogeneity of the studies that were included (Croft *et al*, 2008).

In the period from 2006 to 2009, four meta-analyses were published on epidemiological studies of brain tumors in relation to cell phone radiation exposure: Lahkola *et al*. (2006), Hardell *et al*. (2007), Kan *et al*. (2007) and Khurana *et al* (2009).

A recent meta-analysis covering long-term use of cell phones (equal or more than 10 years) conducted by Khurana *et al* (2009) reported for ipsilateral use an OR of 1.9 (95% CI = 1.4-2.4) for glioma, 1.6 (95% CI = 1.1-2.4) for acoustic neuroma, and 1.3 (95% CI = 0.9-1.8) for meningioma. The authors concluded that *“using a cell phone for more than 10 years approximately doubles the risk of being diagnosed with a brain tumor on the same (‘ipsilateral’) side of the head as that preferred for cell phone use. The data achieve statistical significance for glioma and acoustic neuroma but not for meningioma.”*

Although the authors stated that *“this is a meta-analysis incorporating all 11 long-term epidemiologic studies in this field,”* in fact only 5 of the studies -- 2 by the Hardell group and 3 from the INTERPHONE Study -- were included in the quantitative analysis, because the other papers didn't had cases with more than 10 years of cell phone use.

The meta-analysis by Lakhola *et al* (2006) for studies with more than 5 years follow-up, on the other hand, reported a pooled odds ratio (OR) of 0.98 for all intracranial tumors related to mobile phone use, which is close to unity, i.e. there is no evidence for a differential risk. For gliomas, the pooled OR was 0.96, for meningiomas it was 0.87, and for acoustic neuromas it was 1.07, all within the 95% confidence interval.

Epidemiological Data on Exposure of Children

The fact that more and more children and adolescents have become users of cell phones (the prevalence is already more 40% in children under 15, and more than 90% among adolescents in some countries) and wireless computers has raised strong health concerns, to the point that public authorities in some countries have passed legislation prohibiting base stations near schools, something that has no scientific basis (antenna far fields power densities are too small; furthermore, the exposure of children out of school is not controlled by such legislation. Ironically, the prohibition of use of cell phones by children, however, has not been the subject of legislation until now).

It has been argued by some investigators that children could be more vulnerable to RF, because they have developing organisms and that their head structures might be penetrated more deeply by RF fields (see review by Otto & von Mühlendahl, 2007). In addition, the use of mobile phones between today's children and adults is the longer lifetime exposure of children when they grow older, due to starting to use phones at an early age (Schüz, 2005).

While there are no scientific data that developing organisms are more vulnerable than adults to low-level, RF fields (Kheifets *et al.*, 2005) there are presently no epidemiological studies addressing children and adolescents cancer risks of exposure to RF. One of the reasons is that this is a very recent phenomenon. The other reason is that most cancers are extremely rare in young people. The third factor is that epidemiological investigations that require recall of information by users are not easy to do with children. It has been suggested, however (Kheifets, personal communication, 2010), that they might be in the same order of magnitude, *i.e.*, also not very high, than in adults). Two international studies of brain tumors in children and adolescents are underway, CEFALO (Feychting, 2006) and MOBI-KIDS (Parrish, 2010, see also <http://www.mbkds.com/>).

In conclusion, according to Martens (2005), "*all this makes a definitive answer to the question if children are more sensitive to electromagnetic fields than adults impossible. More consistent research will be needed.*" A precautionary approach, especially with small children, could be the cheaper and more effective option, for now.

Although there is insufficient data to conclude anything about the use of mobile phones by children and its effect on health, some studies indicated an increased risk of leukemia in children living close to strong radio or television broadcast transmitters (Ahlbom *et al.* 2004, Schütz & Ahlbom, 2008). In one case-control study carried out in South Korea involving 1,928 childhood leukemia cases (Ha *et al.* 2007) no association was seen between childhood leukemia risk and the predicted field strengths (OR=0.83, 95% CI: 0.63-1.08). A second case-control study conducted in German municipalities surrounding 16 AM radio and 8 frequency-modulated (FM) radio and television broadcast transmitters (Merzenich *et al.* 2008) involved 1,959 childhood leukemia cases and 5,848 population-based controls. No increased risk was seen for the first exposure decade alone (OR of 0.86, 95% CI: 0.67-1.11), and no distance effect was observed (OR = 1.04 (95% CI: 0.65-

1.67) among children living within 2 km of the nearest broadcast transmitter compared to those living at a distance of 10-15 km.)

Occupational Studies

Intuitively, it is easy to infer that occupational exposure to RF might be a much more serious problem for public health than exposure of the general public, because many workers are exposed on a daily basis to much more intense RF fields, for longer times, so that they receive a far higher chronic and acute “doses” of non-ionizing radiation. Examples of these workers are installation and maintenance technicians of RF antennas, amplifiers and transmitters, radar operators, including police and transit radar operators, operators of microwave plastic welding machines, technicians and health care professionals who employ microwave and RF therapy devices and high intensity field imaging devices, such as magnetic resonance tomography (MRI). So evidence of a causal relationship for cancer would most likely appear in these occupational settings than in others.

While dozens of occupational studies on RF using case-control, cohort and correlation studies were published in the last 50 years, there have been few, if any, well conducted and extensive epidemiological studies on occupational exposure. Most of the studies reviewed by Ahlbom *et al.* (2004) were conducted in the 1990s and early 2000s and had many methodological deficiencies. In almost all of them no or few RF exposure measurements were made, and the group of exposed subjects was categorized only in terms of its job description, duration of exposure and/or distance from transmitters.

The main occupational health outcomes published were:

Total mortality

Neoplasias:, incidence for brain, breast, testicular, ocular melanoma, lung cancers and leukemia

Breckenkamp *et al* (2003) evaluated the methods and results of nine cohort studies dealing with various effects on human health from exposure to RF, published between 1980 and 2002. The size of the cohorts varied between 304 (3,362 person years) and nearly 200,000 persons (2.7 million person years). The occupational exposure groups were workers with dielectric heaters in plastic manufacturing plants, workers with radio devices (professional and amateur), production workers of wireless communication technologies, users of radar devices of the Canadian police and those used by the military. Total mortality, cancer mortality, cancer incidence or other outcomes were estimated. In some of the studies an increased risk for various types of cancer was found in exposed participants, although in different organs. The review concluded that, due to methodological deficiencies of most of the cohort studies, no conclusion could be reached whether an elevated risk for cancer existed for these occupational exposures.

Ahlbom *et al* (2004) similarly reviewed 10 cohort studies, carried out from 1988 to 2002 (with a large overlap with Breckenkamp’s review) and examined brain tumors, incidence of leukemia and relative risk in professionals of several work sectors. Risk ratios for both outcomes were mostly under or around unity, with only 2 out of 14 studies on brain cancer having RRs slightly above unity. They also reported that 6 out of 12 leukemia studies had large RRs, varying from 4.4 to 7.7, two of them Polish studies about military people living

near high power transmitters. According to the reviewers, these large RRs could be explained by rather gross biases and errors, or by confounding factors such as the presence of chemical contaminants. The number of cases also varied widely, ranging from 1 to 69 cases of leukemia and 1 to 44 for brain tumors. The authors also reviewed 3 case-control studies on occupational exposure to RF in relation to brain tumor and leukemia. The majority of RR and SIRs were below or around unity, showing no association.

More recently, the German branch of the INTERPHONE case-control study carried out an occupational case-control study (Berg *et al*, 2006). No significant association between occupational exposure to RF and brain tumors was found (OR for glioma of 1.21 and for meningioma 1.34, both not statistically significant).

So far, the balance of these epidemiological studies suggest higher risks of occupational cancer risks due to chronic exposure to apparently higher power densities of RF, for diverse groups such as radar operators, telecommunication installation and maintenance technicians, and others. The outcome that causes most concern is an increased rate of leukemia. No consistent effects have been demonstrated, but they could not be refuted either, due to the low quality and short duration of the cohort and case-control studies carried out so far.

The feasibility of carrying out cohort studies of occupational risks, however, is low (Breckencamp *et al*, 2009), due to the small numbers of exposed subjects or due to exposure levels being only marginally higher than those of the general public, small duration of exposure due to job changes or technological changes, great variability regarding the documentation of the use of individual protection equipment by workers, and the impossibility of separating RF exposure from other environmental risks (such as in industrial plastic sealers, which are also exposed to plastic vapors).

In Latin America, there is currently a growing concern about the health of technicians who do maintenance work very near “live” antennas (i.e., which are not disconnected during maintenance work). First- and second-degree burns by touching waveguides have been reported. Although required by law to cut off power to the antennas during this work, telecom operators usually ignore it, due to the fear of provoking an imbalance in the network service architecture. There seems to be little danger, however, if a modicum of caution and use of individual protection were adopted, such as heavy clothing, gloves, helmets and insulated materials. Alanko & Hietanen (2007) surveyed and evaluated RF power in transmitting antenna arrays for mobile phone networks, radio and digital TV substations and amateur radio, close to the access ladders. They reported that all measured values where workers would normally be located were below ICNIRP occupational reference levels.

Curiously, but easy to understand why, is the position of occupational physicians in charge of RF occupational hygiene programs in companies. A survey with more than 200 occupational physicians in Brazil (Sabbatini *et al.*, 2008, unpublished manuscript, personal communication) showed that: 1) the concept of non-ionizing radiation for most physicians is related to occupational exposure to excessive heat and light, to the sun, to coherent light (therapeutic and industrial laser), microwave plastic welding, industrial use of UV, arc welding, etc. 2) few physicians have any knowledge about occupational exposure to RF used in radiocommunication and its risks, even those who work in this industry; 3) They consider that this physical agent is too weak, compared to other much more aggressive and dangerous ones, to worry about them.

Analysis of time trends

Some would say that the extraordinary growth and spread of mobile communications is the largest experiment ever made by humans. This means that billions of people are exposed daily to cell phone and base station RF fields, and that millions have been doing so for 20 years or more (albeit at much lower levels than present use). It is important to remark, also, that high power transmission antennas for radio are in existence for more than a century already, and that radar and TV transmission dishes and towers exist for more than 50 years. Therefore, the exposure of the general population to artificially generated RF is not a recent thing.

Thus, by using only common sense thinking, one would expect that, even with relative risk ratios slightly above unity, epidemiological science would already be able to detect a considerable increase in the number of new cases of cancer every year, should RF exposure be detrimental. One should not forget that the emergence of AIDS was detected with a number of cases not much higher than 60, in the USA. The question, therefore is: where are these new cases of cancer due to a cause-effect link between exposure to the several RF sources in the environment and the induction and promotion of neoplasias?

One of the useful by-products of estimating risk ratios and incidence ratios by means of methodologically rigorous and highly consistent cohort studies is the possibility of predicting the absolute number of disease cases that could be found now or in the future. This has been done successfully with tobacco smoking, for instance, and it was of great value for many public health and prevention programs, as well for planning cost of service, impact of preventive measures, and so forth.

Curiously, this has been remarkably absent from epidemiological RF studies. We should try to test if the predictions underestimate or overestimate reality. One of the few examples of this kind of analysis is a study of the time trend of incidence of uveal melanoma by Johansen et al. (2002), which, despite a four-fold increase in the incidence of this tumor in Denmark in the preceding decade, did not find a correlation with increase in the use of cell phones

So another tool of epidemiology comes to rescue: the analysis of time trends of selected diseases. Brain cancer is still a rare disease when considered in relation to the overall population. In the USA, for example, Deorah *et al* (2007) did such an analysis for all kinds of brain cancers, adjusted for age. Its incidence increased until 1987, when the annual increase (as percent) decreased from 1.68 to 0.44%. This period coincided almost exactly with the large scale introduction of mobile telephony in the country, but this probably has no meaning if the latency period of brain cancers is longer than 20 years. Obviously, these variations in incidence could have nothing to do with environmental factors: they could be due simply to the increase of diagnosed cases by the increasing use of better medical technologies for its detection, such as the case of brain computed tomography (which started in the 80s), a larger coverage of tested population, the introduction of preventive programs, etc.

A few recent studies have addressed this point. For instance, Muscat *et al.* (2006) analyzed the incidence rate of cancers of the CNS from 1972 to 2002. They concluded that these rates did not change appreciably during this period, despite an exponential increase in mobile phone subscribers since 1984.. The results by Deorah *et al.* (2006) also failed to support the hypothesis that a risk of brain cancer and survival in the USA would

add more cases due to the increase of the exposed population. In Switzerland, brain tumor mortality rates, as in many other countries, have remained stable in all age groups (Röösli *et al*, 2007). Age-adjusted incidence and mortality of CNS cancers are actually falling in most countries. In the Röösli study cited above, the annual rate of new cases of brain cancer from 45 to 59 years of age in the period of 1987 to 2002 was -0.3% for men and -0.4% for women. There is, however, a slight increase in the incidence of brain cancer among younger people, but the reason for this is presently unknown.

Deltour *et al* (2009) examined the time trends in brain tumor incidence from 1974 to 2003, using data from the national cancer registries. The incidence rate of glioma increased 0,5% per year (C.I. 0.2-0.8%) among men and by 0.2% per year (C.I. -0.1-0.5%) among women, and that of meningioma increased by 0.8% per year (95% CI = 0.4% to 1.3%) among men, and after the early 1990s, by 3.8% per year (95% CI = 3.2% to 4.4%) among women. The authors concluded that *“no change in incidence trends were observed from 1998 to 2003, the time when possible associations between mobile phone use and cancer risk would be informative about an induction period of 5-10 years.”*

It is important to note, however, that the calculus of statistical association between time trends of relevant variables is fraught with difficulties. Any two variables that go up or down in synchrony will generate a spurious high association or correlation, without necessarily being causally related. In addition, since the time delay of cancer causation is usually very large, an upward surge of cancers putatively caused by increasingly massive populations exposed to RF due to mobile communication would occur, if ever, still somewhere in the future. The majority of papers examined in the present review, however, give an indication that this increase has an extremely low plausibility.

Conclusions from Cancer Epidemiological Studies

From our review of the literature on epidemiology, there seems to be a scientific consensus that there is no firm evidence for an increased cancer risk and mortality among cell phone users. Regarding cancer incidence, the recent results (2007 and 2008) of extensive cohort studies and case-control studies (the INTERPHONE project), have provided us with the best epidemiological evidence so far for an absence of any risk, up to 10 years of continuous use of cell phones. But the data for long term heavy users (brain cancers may have long latencies of 30 years or so) is still lacking.

Regarding the possible association between exposure to base station RF and health effects, this has been impossible to prove or disprove so far, due to the lack of good quality and extensive studies, and substantial methodological difficulties. Unfortunately, the scientific status of epidemiological research in this area rests on very shaky and unwarranted ground, because, in contrast to other better established areas of investigation, *“the RF research questions are not driven by a specific biophysical hypothesis but rather by a general concern that there are unknown or misunderstood effects of RFs”* (Ahlbom *et al*, 2004).

The conclusions are best expressed by statements by the following authors and expert committees:

Ahlbom *et al*, 2004 (ICNIRP): *“Overall, although occasional significant associations between various types of brain tumors and analog mobile phone use have emerged (often seen after multiple testing), no single association has been consistently reported across*

population-based studies. The timing of epidemiologic studies and the lack of knowledge about actual RF exposure to the brain from mobile phone use to date (...) militate strongly against current ability to detect any true association. Thus current evidence is inconclusive regarding cancer risk after heavy RF exposure from mobile phones. (...) Results of epidemiologic studies to date give no consistent or convincing evidence of a causal relation between RF exposure and any adverse health effect. On the other hand, these studies have too many deficiencies to rule out an association. ”

Ahlbom et al, 2009 (ICNIRP): *Despite the methodological shortcomings and the limited data on long latency and long-term use, the available data do not suggest a causal association between mobile phone use and fast-growing tumors such as malignant glioma in adults (at least for tumors with short induction periods). For slow-growing tumors such as meningioma and acoustic neuroma, as well as for glioma among long-term users, the absence of association reported thus far is less conclusive because the observation period has been too short.*

SCENIHR (2007): *The epidemiological evidence indicates that mobile phone use of less than 10 years does not pose any increased risks of brain tumors or acoustic neuroma. For long term data are sparse and the conclusions are therefore uncertain and tentative – however, from the available data it does appear that there is no increased risk for brain tumors in long term users, with the exception of acoustic neuroma for which there is some evidence of an association. (...) In conclusion, no health effect has been consistently demonstrated at exposure levels below the ICNIRP limits established in 1998. However, the data base for this evaluation is limited especially for long term low level exposure*

WHO/IARC (International Agency for Research on Cancer) World Cancer Report 2008. <http://www.iarc.fr/en/Publications/PDFs-online/World-Cancer-Report>

“Radiofrequency radiation emitted by mobile telephones has been investigated in a number of studies. There is some evidence that long-term and heavy use of mobile/cellular phones may be associated with moderate increased risks of gliomas, parotid gland tumors, and acoustic neuromas; however, evidence is conflicting and a role of bias in these studies cannot be ruled out.” (p. 170) “With reference to radio frequency, available data do not show any excess risk of brain cancer and other neoplasms associated with the use of mobile phones.” (p. 170). Concerning brain tumors: “After 1983 and more recently during the period of increasing prevalence of mobile phone users, the incidence has remained relatively stable for both men and women.” (p. 461)

The INTERPHONE studies which were published so far mostly do not support high associations between brain tumors and use of phone cells handsets, at least for gliomas, meningiomas and acoustic neuromas, as well as for parotid glands tumors. The large expectations regarding the INTERPHONE studies, therefore, have been widely justified by its results, which seem to be those with the highest methodological quality until now. Large scale cohort studies, such as COSMOS (Schüz, 2006), as well as more community exposure studies should be the next big project to solve lingering doubts about risk assessment in various age groups, particularly children.

Other Symptoms and Diseases

There are extremely difficult methodological problems to surmount for epidemiological studies aiming at evaluating risks related to RF exposure and other common diseases. An

important reason is that, as opposed to cancer incidence studies, most of the candidate diseases are not subjected to mandatory registration, and that patient medical records are incomplete, often inaccurate and contributed to by so many health care providers, that retrospective data based on patient information are generally unreliable and inaccurate.

Cardiovascular, gastrointestinal, endocrine, nervous system, and reproductive disorders are the main areas of interest, but have not been adequately investigated.

Ahlbom *et al.* (2004) have reviewed the effect of several kinds of occupational exposure to far electromagnetic fields on other diseases than cancer. The main independent variable was job description in most of the studies, and the number of subjects per study was usually very small.

In another recent review of epidemiological studies of the effect of exposure to electromagnetic radiation emitted by base stations of cellular antennas, Rösli *et al.* (2009) analyzed 17 articles that were considered of satisfactory scientific quality, of which 11 were epidemiological studies and six were of controlled exposure. Most articles (14) examined the association between exposure and well-being or nonspecific symptoms of ill health (malaise, headache, fatigue, nausea, etc.), as reported by the patients. Most studies that attempted to study the acute effects of exposure found no association with symptoms during or shortly after exposure to radiation from base stations. Studies conducted in the laboratory found no consistent patterns of response, suggesting that the reported symptoms had nothing to do with the exposure itself. Epidemiological studies have shown no evidence that people living near base stations are different from those who do not live near them. The authors claim that the exposure of humans under these conditions of fields above 1 V / m almost never occurs, so it is not possible to attribute effects.

Cataracts: They are a plausible health outcome due to heating, and several previous studies had reported a possible increase in incidence of cataracts in several kinds of workers that deal with high intensity RF pulses, such as radar, TV and radio transmitter. The quality of such early studies, however, was low (WHO, 1993). In Ahlbom's review, four of these earlier studies from 1965 to 1984 provided no evidence of an increased risk for cataracts in the studied categories. Confounding effects, such as chronic exposure to sunlight without protective eyeglasses (a well-documented risk) were not controlled for.

Reproductive risk: Several parameters have been evaluated in relation to occupational RF exposure in 17 studies from 1975 to 2000: quality of semen, fertility, spontaneous abortion, stillbirth, low birth weight and birth defects. In 10 studies, cases were physical therapists, both male and female, who often used microwave ovens and RF heating devices without any protective measures. Radar operators and military personnel using high power RF emitters comprised the rest. No studies on maintenance technicians of RF antenna arrays were investigated. The majority of studies could not prove any large effect, and showed relative risk ratios under 1.3, except for some evidence for a reduction in the number of spermatocytes in three studies. According to Ahlbom, "*given the well-known susceptibility of spermatogenesis to even subtle heating, the possibility of reduced fertility in exposed men is reasonable to evaluate*".

Cardiovascular disease: There are very few epidemiological investigations of good quality on the incidence and risks of cardiovascular diseases, such as hypertension, ischemic heart disease, etc., in relation to RF exposure. A biophysical and etiological link which might explain these diseases are difficult to find, and all other numerous important

risk factors for cardiovascular diseases, such as heredity, chronic stress, smoking, diet, exercise, dislipidemias, etc., have not been taken into account in most of the published studies on RF effects. A large cohort study with almost 200,000 Motorola employees (Morgan *et al*, 2000) potentially exposed to RF showed, as expected, the so called “healthy worker effect”, i.e., it was observed a lower mortality, hospital admissions, and incidence of cardiovascular diseases in exposed than non-exposed individuals. The average relative risk was 0.5, only, although the characterization of exposure was not clear in the study.

Behavioral changes: Due to the highly unreliable self-reporting outcomes, very few case-control and cohort epidemiological studies have been carried out on behavioral changes. One exception is Divan *et al* (2008), who examined the association between prenatal and postnatal exposure to cell phones and behavioral problems in young children within a prospective/retrospective large cohort study. Mothers of 13,159 children in Denmark completed questionnaires on their use of cell phones during pregnancy, as well as current cell phone use by the child. The authors reported adjusted OR ratio of 1.8 for behavioral problems observed in children who had prenatal and postnatal exposure to cell phone use. The conclusion was that “*exposure to cell phone use was associated with behavioral difficulties such as emotional and hyperactivity problems around the age of school entry.*” The authors state “*observed associations are not necessarily causal (...) and confounding by unmeasured causes of behavioral problems could have produced these results. Furthermore, this is the first study of its kind (...) and awaits replication.*”

Nonspecific symptoms: Diverse groups of people living near base stations for mobile telephony have reported on a wide range of symptoms, such as fatigue, unwellness, vertigo, dizziness, sleep disturbances, headaches, gastrointestinal symptoms such as nausea and diarrhea, loss of appetite, visual symptoms, decrease in libido, loss of memory and concentration and depression. It must be noted that these are very common symptoms for many diseases or as isolated events without a specific cause. They have also been associated with mild mental disturbances, stress, anxiety, depression, psychosomatic manifestations (somatization) and other affective disorders. Experimental designs (called provocation studies) are better suited to investigate the appearance of these symptoms in relation to RF exposure in individuals, but are able to evaluate only short term exposure. The epidemiological investigations suffer from several methodological problems which usually invalidate its results, mainly due to sampling errors, strong recall bias, and others, which are discussed below. Nevertheless several such low-quality cross-sectional studies have been carried out (Santini *et al*, 2002, 2003; Navarro *et al*, 2003), causing considerable alarm among the population and eliciting responses from public authorities. No case-control or cohort studies on this subject have been published. Cross-sectional studies are inadequate. In addition, the studies were not blinded, opening the opportunity to several bias errors. The survey carried out by Hutter was a little better designed than Santini's and Navarro's .

More recently, a research group in Germany has carried out a population-based, cross-sectional study investigating adverse health effects of mobile phone base stations (Berg-Beckhoff *et al.*, 2009). In phase 1 of the study, a national survey of more than 30,000 respondents to a postal questionnaire were investigated as to general health and complaints in relation to proximity (up to 500 m) to base stations. About 18% of respondents were concerned about possible health effects, while an additional 10% attributed their health problems to the base stations. In the second phase of the study, a field measurement of RF fields was performed for about 3,000 respondents. No correlation

was found between proximity to base stations and health complaints, but those who had sleep disturbances complained more.

Schüz et al. (2009) evaluated nervous system conditions, other than cancer, in the Danish cohort study of more than 420,000 inhabitants, both short- and long-range phone users, by using hospital-based records. Phone users had a 10 to 20% higher risk of migraine and vertigo, and a 30 to 40% decreased risk of epilepsy, dementia and other degenerative disorders of the nervous system, such as Alzheimer, Parkinson, amyotrophic lateral sclerosis, multiple sclerosis, etc. The results are difficult to interpret however, because only a fraction of patients with prodromal symptoms show up in the hospitalization records (simple vertigo and headaches are not usually diseases that require hospitalization), and because several biases could be in operation in regard to the reliability of subscriber records of cell phone use.

The Nocebo Effect

In fact, concern about health effects from EMF seems to result from media reports, eliciting in some persons a number of psychosomatic symptoms and signs which are similar to other anxiety disorders, such as the panic syndrome (Rööslí, 2008). This is a kind of nocebo effect (Bonneux, 2007) is opposite of a placebo effect and it is sometimes extremely detrimental to the quality of life of affected persons, sometimes impeding normal work. Rööslí (2008) concluded that

“the health hazards due to the maintenance of environmental scares by false-positive studies have been neglected. The nocebo hypothesis states that expectations of sickness cause sickness in the expectant individual. Maintaining anxiety by fostering doubts in gullible populations about the quality of the environment they live in may cause serious mental illness. Anxiety caused by health scares is an increasing public health problem, which should be addressed in its own right.

Using a personal RF dosimeter would permit a better measure of RF exposure allowing for correlations with subjective symptoms, in a way very similar to the Holter ECG recorders used in cardiology diagnostics. Recently the first study using this approach was published (Thomas *et al*, 2008). It did not find any statistically significant association between RF exposure and chronic symptoms or between the exposure and acute symptoms.

Epidemiological Studies in Latin America

We have not found any significant epidemiological study on the effects of high-frequency electromagnetic fields on human health. In São Paulo, Brazil, a multi-institutional research group has been established for the Extreme Low Frequencies (ELF) generated by electric power transmission lines.

Main Conclusions about Epidemiological Studies

We conclude, therefore, that current published RF epidemiological studies published so far have not shown any reproducible adverse health effect, and that numerous methodological flaws, along with only the few outcomes examined so far, do not allow for firm conclusions, particularly as it relates to children. Our conclusions are in line with those from other

august international and national bodies of experts, as official statements such as:

European Commission (2009). Health Effects of Exposure to EMF. Opinion of the Scientific Committee on Emerging and Newly Identified Health Risks (SCENIHR) (p. 4). http://ec.europa.eu/health/ph_risk/committees/04_scenihhr/scenihhr_opinions_en.htm

- *“It is concluded from three independent lines of evidence (epidemiological, animal and in vitro studies) that exposure to RF fields is unlikely to lead to an increase in cancer in humans.”*

The Netherlands, Health Council (2009) Annual Update 2008:

- *“The Committee further discusses the relationship between electromagnetic fields and brain activity and that between electromagnetic fields and health symptoms. In both cases the Committee concludes that there is no scientific evidence that exposure to environmental levels of radiofrequency electromagnetic fields causes health problems.”*
<http://www.gr.nl/index.php>

ICNIRP (2009): ICNIRP statement on the “Guidelines for limiting exposure to time-varying electric, magnetic, and electromagnetic fields (up to 300 GHz)”

- *“..it is the opinion of ICNIRP that the scientific literature published since the 1998 guidelines has provided no evidence of any adverse effects below the basic restrictions and does not necessitate an immediate revision of its guidance on limiting exposure to high frequency electromagnetic fields.”*
<http://icnirp.org/documents/StatementEMF.pdf>

French Agency for Environmental and Occupational Health and Safety (2009)

- *“..the currently available experimental data do not indicate short-term or long-term effects from RF EMF exposure, nor do current epidemiological data point to effects from short-term exposure. Questions remain for long-term effects, the group states; however, no biological mechanism has been established to support the presence of long-term harm.”*
http://www.afsset.fr/upload/bibliotheque/964737982279214719846901993881/Rapport_RF_20_151009_1.pdf

And finally, from the most authoritative source, the WHO EMF Project, which has reviewed thousands of published papers on all aspects of EMF fields and health:

World Health Organization (2007)

- *“Despite extensive research, to date there is no evidence to conclude that exposure to low level electromagnetic fields is harmful to human health.” (Key Point #6)*
<http://www.who.int/peh-emf/about/WhatisEMF/en/index1.html>
- *“To date, all expert reviews on the health effects of exposure to RF fields have reached the same conclusion: There have been no adverse health consequences established from exposure to RF fields at levels below the international guidelines on exposure limits published by the International Commission on Non-Ionizing Radiation Protection (ICNIRP, 1998).”* Children and Mobile Phones: Clarification

statement (second paragraph)

http://www.who.int/peh-emf/meetings/ottawa_june05/en/index4.html

Fact Sheet #304: Electromagnetic fields and public health: Base stations and wireless technologies (May 2006)

<http://www.who.int/mediacentre/factsheets/fs304/en/index.html>

- *“Conclusions: Considering the very low exposure levels and research results collected to date, there is no convincing scientific evidence that the weak RF signals from base stations and wireless networks cause adverse health effects.”*

Fact Sheet #193: Electromagnetic fields and public health: mobile phones (May 2010)

<http://www.who.int/mediacentre/factsheets/fs193/en/index.html>

- *“Several large multinational epidemiological studies have been completed or are ongoing, including case-control studies and prospective cohort studies examining a number of health endpoints in adults. To date, results of epidemiological studies provide no consistent evidence of a causal relationship between radiofrequency exposure and any adverse health effect. Yet, these studies have too many limitations to completely rule out an association (...) The increasing use of mobile phones and the lack of data for mobile phone use over time periods longer than 15 years warrant further research of mobile phone use and brain cancer risk. In particular, with the recent popularity of mobile phone use among younger people, and therefore a potentially longer lifetime of exposure, WHO has promoted further research on this group.”*

Strong evidence and knowledge about the relationships between personal exposure to EMF, such as those used in RF broadcasting and communication, is still limited, mostly due to the relative lack of extensive and well controlled epidemiological studies, a restricted set of health outcomes that have been studied so far, and significant methodological difficulties posed by such studies. Studies that have indicated a positive association are sparse and are outweighed by studies with negative results. There is no satisfactory consistency among studies. Well conducted meta-analyses in relation to the incidence of head and brain cancer suggest no risk exists (e.g., Lakhola *et al.*, 2006),

This applies to neoplasia-related outcomes, such as brain and head/neck cancers, for adverse reproductive outcomes, as well as for other symptoms and detrimental effects on health that were studied, such as cardiovascular, reproductive and ocular disorders, effects on the nervous system and the so-called Electromagnetic Hypersensitivity Syndrome (EHS). Empirically calculated risk ratios have been in its majority below unity, or, if positive, with relatively low values, which are difficult to interpret due to the low incidence of these diseases in the samples studied.

This lack of evidence is particularly acute in long term epidemiological studies relating to exposure to base stations. The low levels of RF used by modern digital devices suggest that extremely long latencies for any health manifestation from chronic exposure are to be expected, but no study has so far been completed to address latencies longer than 20 years. Thus, longitudinal, prospective epidemiological studies spanning decades of high quality observation will have to be carried out before any evidence is provided in this respect. Furthermore, there are no epidemiological data about specific groups of users,

such as children.

Statement of the Latin American Committee

The members of the Committee concluded that, in view of the methodological difficulties and great costs involved in this kind of research, that it is not a priority for the region right now, and that they could be pursued by more resourceful countries, such as is being done within the INTERPHONE project. It is clear that their results could be extended to Latin American countries. The Committee suggests that the health priorities for funding research and care are in a different direction, due to the huge human and economic costs of diseases such as dengue fever, malaria, Chagas disease, tuberculosis, AIDS, malnutrition, developmental disorders, and others, which are still prevalent, but poorly funded and neglected by pharmaceutical companies and the medical establishment of the more developed countries.

Methodological Issues of Epidemiological Studies

Ahlbom *et al.* (2004) called attention to the many difficulties that surround observational epidemiological studies of adverse health outcomes of medium to long term exposure to RF fields. Other authors, such as Auvinen *et al.* (2006) have also commented on these points, arguing that considerable improvements must be made in the factors that affect the validity of epidemiological studies on health effects of mobile phone use, such as in study design, risk assessment and exposure assessment.

For the sake of qualifying the reviewed epidemiological studies, we will briefly mention some of the main points here.

Diversity and contribution of exposure sources: Valberg *et al.* (2007) indicated that the human body absorbs about 5 times more of the RF energy from FM radio and television frequencies (around 100 MHz) than from base station frequencies (around 1–2 GHz). There are few reasons for a study to single out a certainty of exposure to a mobile phone base station, except exposure prevalence, but this does not rule out other sources unless a detailed spectral analysis is carried out prospectively during the time of exposure. Thus, there is little evidence that presently justifies epidemiological studies being restricted to adverse effects of radio waves from mobile phone base stations while neglecting radio waves at other frequencies produced by different transmitters near subjects (Schüz *et al.*, 2000). Assuming that groups differ in this exposure only by the proximity to a base station mast, for instance, is unwarranted if the power distributions for other frequency bands are not actually measured in the locations where each patient lived. In addition, since subjecting people to a single frequency band for any significant length of time is impossible, the determination of the contribution of each band to overall risk remains a difficult proposition at best (Neubauer *et al.*, 2007). In fact, some authors suggest that “*it is virtually impossible to eliminate exposure to RF from other sources for studying the isolated effects of cell phones on health.*” (Kohli *et al.*, 2009); hence a causal nexus cannot be inferred at all for a specific effect of RF due to a single source (e.g., mobile telephones or base stations).

Poorly estimated population exposures: this is the single most criticized methodological weakness of epidemiological studies. With the techniques used by the studies reported so far, particularly for community and occupational exposure, it is exceedingly difficult to determine with any degree of reliability the intensity of the independent variable, which is

Specific Absorbed Rate (SAR) for different parts of the body, even when field power densities are measured. Many studies simply used a job description as an indicator of exposure (Ahlbom *et al.* (2004), or were based on distance to the nearest RF source to determine cases and controls, or relied only on theoretical calculations. Large ranges of variation of exposure, either in intensity or time were combined, even in apparently well designed studies. Therefore, the reliability and strength of evidence of these epidemiological investigations is very low and cannot be trusted as firm evidence. Breckenkamp *et al.* (2008) carried out a comparison between calculated exposures based on technical data of base stations nearby the subjects and the measured levels using dosimeters and concluded that there is a low correlation (0.28), specificity and sensitivity, that calculated distances from maps introduced a higher uncertainty than actually measured ones, and that only individual dosimetry should be used in epidemiological studies of community exposure, due to the large errors introduced by other proxies of exposure. Auvinen *et al.* (2003) suggested that observed “effects” or “no effects” could have been mostly random in several studies. In addition using more objective data than self-reported cell phone use is critically important for experimental as well-designed epidemiological studies. The number and duration of calls made, by retrieving information from the telecom providers is such a measure, but it is difficult to ascertain who was actually using the phone when the call was made, or if the call was made using a earphone or a loudspeaker (hands-free) away from the head. Schüz & Johansen (2007) found a 60% agreement between self-reported use (a measure which suffers from other kinds of recall bias itself) and subscriber records, which represents a sufficiently large margin of error for calculating risk ratios with small number of subjects. Another person might be using the cell phone, too.

Variation of transmitted power: The power emitted by the cell phone might also vary substantially from call to call, depending on the distance to the base station at the time of the call, the place where the phone is used (inside a car, for example), among other factors. For instance, Lönn *et al.* (2004) measured output power of handsets in zones of different degrees of urbanization. In rural areas where base stations are sparse, the output power level used by mobile phones are on average considerably higher than in more densely populated areas. The same applies for community exposure studies: several studies have shown that is totally unwarranted to assume that any given building has even approximately the same power density in all locations inside it: people moving around a house or apartment will be subjected to continuously and widely fluctuating exposures. The main consequence of this fact is that it cannot be assumed that only because different people live at the same distance from a base station antenna they will be subjected to the same average SAR.

Inadequacy of proxy measures: Several methodological investigations have challenged the adequacy of proxy or surrogate measures of exposure, such as time of use, average number of calls, and even duration. Morrissey (2007) for example, found that they correlate rather poorly with RF exposure, because there is a large variability during a single call, between calls, between individuals, different age groups and geographical locations. There are also large differences in transmitted power between different models of cell phones. Inaccuracy of recalling time of use can be as large as 60%. For community exposure studies, determining the power density of RF fields is also essential, because some field surveys have shown a very large variation between different living areas (e.g. Neitzke *et al.*, 2007).

Other forms of mobile communication: Using a cell phone is a catch-all term which may

not reflect the degree of direct exposure to RF just by using in touch with a side of the head several times per day, as many studies seem to infer. Not only it is impossible to know from company records, or from proxy reporting how often people make or receive hands-free calls (thus decreasing exposure of the head), but how often they are using text messaging, Internet navigation, emailing, listening to music with earphones, or whatever other uses that avoid close contact and are increasing at very fast rates, particularly among the younger generations. Since these other uses vary enormously with time Different among age groups, socio-economic and educational levels and even among individuals, often being influenced by subtle factors such as cost, matching may not be possible and randomization may not be guaranteed in epidemiological studies.

Multiple and unaccountable sources of exposure: Other biases that are difficult to control for, particularly for register-based retrospective cohorts, are caused by another major trend in mobile communication; many users have multiple cell phones in their names (or not) or under unnamed corporation accounts, and use them in a haphazard, impossible to track, manner. In many countries, prepaid, unidentified cell phones represent more than 80% of all lines, and a large part of the population of users owns both post-paid and pre-paid phone lines, or may operate with two providers, and even have two-chip cell phones. Record linkage procedures will not work in all these cases, and evaluating exposure using company records will invariably under-estimate exposures.

Long-term temporal changes in exposure levels: Poor exposure assessment has also been due to another factor that has been often ignored by researchers in mobile communication: the rapid change in telecommunication technologies. A person who has used a mobile phone for 10 years or more has probably been the owner of several handset models with very different exposure parameters along this time. Recent data show that two thirds of American users substitute their phones after an average of less than two years use, and that this pace is accelerating, being higher for the younger generation (International Communication Research, 2010). For instance, in Brazil, 70% of users in a national survey said they wanted to buy a new phone in 2010. In 2008 this percentage was 32%. (Gilsogamo, 2010). First-generation (analog) cell phones were in wide use until late nineties and exposing users to RF fields which were 5 to 20 times more intense and employed larger external monopole antennas compared to the latest all-digital models, and, as technology evolves, the trend is towards even lower exposure levels.

In some places analog phones are still used; or this mode is entered automatically when in roaming mode in certain places, but the largely complete global change to GSM, CDMA, TDMA and other digital transmission technologies took place in less than ten years. In the United States, AMPS analog technology was commercially introduced in 1983, iDEN and CDMA, the first digital technologies, in 1994 and 1996, respectively, and second generation (2G) phones in 1997. The GSM standard of digital mobile telephony started in 1992 in several European countries, and within two years it had achieved a global reach, arriving in the USA in 1997. Third and fourth generation mobile technologies were launched worldwide in 2003 and 2009, respectively, and use remarkable lower RF fields and its base stations are also less intense and more closely spaced. Micro- nano- and femto-cells, with very low radiation, are now becoming the norm.

Adding to the complexity of exposure assessment, mobile communication the number of users has increased many times the total time of phone use in the last 20 years. For example, in 1998 the average consumer used his or her phone 122 minutes per month. Two year later, this had almost triplicated to 320 minutes per month, and now may be

above 600 minutes per month for some heavy users, such as the new category of “cell phone junkies”.

The conclusion is that the high inaccuracy in measuring the real values of the independent variable with such a wide margin of error make most of the studies difficult to interpret and to reach the truth, Furthermore, the exposure assessment picture is very complex and will become more so in the future. Since rate of adoption and cultural differences are wide, pooling results of several countries by using only self-estimates of time and frequency of use, or even company records, such as in the INTERPHONE studies, may not provide an appropriate estimate of phone use.

Unmatched control groups: Conducting epidemiological research that compares cell phone users to non users will become impossible in the future, because there is an increasing difficulty in finding people who are not users of this ubiquitous communication technology, particularly among the youth. Sabbatini (2010). A recent survey of cell phone users in three cities of different size in Brazil, found that penetration is lower among the very poor and the very old, and it is now more than 100% in the age bracket from 18 to 30 years. In this situation, unavoidable selection biases will introduce large errors, since control groups will be different from cases in many ways, regardless of efforts to match them according to major variables.

Small numbers of cases: except for two large cohort studies, most of the epidemiological investigations were made using case-control approaches, which use a smaller number of cases (subjects with the disease). Although the later methods can be sensitive enough to detect significant associations even with relatively small numbers of subjects, there are several possible biases and statistical anomalies when investigators have been unable to gather sufficient case data, such as when the incidence of cancer investigated was very rare (some studies were based in 1 to 3 cases only). Many statistical tests become unreliable with such exceedingly low numbers, and risk ratios slightly above unity might turn out to be significant by pure chance or, more likely, large effects can be missed. Monte Carlo simulations have shown that highly asymmetric contingency tables are very sensitive to small variations in the numbers of patients who presented the disease.

Small number of spatial samples: Some of the community exposure studies which have been published were not included in our review due to the fact that they investigated cases of cancer clusters in one single location around the cell phone masts, only, and compared them with controls in a different location, quite away from a mast. Of course, if care is not taken to exclude or to match for other factors, such as ionizing radiation seepage (underground radon, for example), toxic dump remains, age, inheritance (e.g., the existence of family or ethnic groups living in the same area), etc, the results cannot be adequately interpreted (CDC, 2010). In one of the papers recently published by an Austrian researcher, a spatial association of cancer incidence and living proximity of affected subjects to a base station was discovered. Unfortunately, it was announced that the antenna in question was disconnected, and the paper had to be retracted. This exemplified the hazards of careless epidemiological research and statistics with a small number or a single location.

Selective investigation in response to the appearance of cancer clusters. Cancer clusters are known to occur, as the result of random spatial and time phenomena. Thus, reacting with retrospective studies prompted by community reaction to these clusters, a very frequent response, is a bad research practice, because a causal-epidemiological

nexus is very difficult to arrive by. Not to mention that they often do not have an underlying cause.

Small number of outcomes: Most of the published studies have focused on a small number of health outcomes, such as tumors of the head, neck and central nervous system. The selection of these outcomes may leave out other outcomes or endpoints that might be significant (Ahlbom *et al.* (2004) . In fact, rarer tumors may have been left out of the epidemiological studies, although their incidence might be better correlated to power density distribution in the brain. According to the INTERPHONE October 2008 summary by IARC, *“because exposure to RF from phones is localized, if a risk exists it is likely to be greatest for tumors in regions with greatest energy absorption. The spatial distribution of RF energy in the brain was characterised, using results of measurements made on over 100 phones used in different countries. Most (97–99% depending on frequency) appears to be absorbed in the brain hemisphere on the side where the phone is used, mainly in the temporal lobe. The average relative SAR is highest in the temporal lobe and the cerebellum and decreases very rapidly with increasing depth, particularly at higher frequencies. Analyses of risk by location of tumor are therefore essential for the interpretation of results studies of brain tumors in relation to mobile phone use (Cardis et al, 2008).* Therefore studies purporting to better characterize the three-dimensional location of brain tumors in relation to RF exposure should be carried out in the future.

Multiple hypothesis testing is common in cancer epidemiological studies related to EMF exposure. However, this increases the chance of obtaining false positive associations and should be avoided. Another bias is created when Investigators often focus on the most significant associations generating further biases. Particularly in small studies, apparently strong associations may be spurious and not supported by subsequent studies. (Pocock *et al*, 2004).

Differential effects of confounding variables: This factor may be, in some measure, a consequence of others, such as small sample size, because the large diversity of potential confounding variables makes reliable stratification, matching or selection, the classical devices for reducing variability, a difficult task (Breslow & Day, 1980). Modern statistical methods such as conditional multiple regression analysis may alleviate the problem, but the fact still remains that investigators are often unable to determine if case and control groups differ from each other in terms of the operation of confounding variables. One example of how these variables can distort results has been the INTERPHONE validation study in Germany (Schlehofer *et al*, 2007), which discovered that exposure to loud sounds, smoking and hay fever were significant risk factors for acoustic neuromas, but not exposure to ionizing and non-ionizing radiation (except for people who were irradiated for medical purposes on head and neck, with an OR of 6.05 (Blettner *et al*, 2007)). A case control study by Edwards (2006) confirmed the higher risk (OR of 2.12) of acoustic neuroma for people hearing loud music for 13 years or more. Studies such as those by the Hardell group, which did not matched these and other variables in the control and case groups might thus reach false conclusions. There might be an explanation, for example, for the elevated relative risks for ipsilateral acoustic neuroma in several epidemiological studies, such as those by the Hardell research group, as well as thos of INTERPHONE, since it is possible that the ear damage caused by prolonged and heavy user of cell phones could not be explained solely by RF exposure, if high volume sounds cannot be separated as to its effects.

Latency bias: Besides the latency between start of exposure and diagnosis of disease,

which is inherent to many diseases, including cancer, another methodological difficulty in epidemiological studies is the latency between start and detection of disease (by mean of its manifestation and subsequent diagnosis, which may also introduce a delay). This can be very large in cancer due to exposure to environmental agents (e.g., Gofman, 1990). In some cancers it may actually exceed the life span of subjects, depending on their age at the start of the study. Due to difficulties in determining the true latency period, usually the two latencies are combined into one. This latency bias, therefore, as a failure to adjust for the latent period in observational studies (Gail & Bénichou, 2001), may introduce differential systematic errors into the study and affect the results in several ways. For example, in cohort studies, the study may finish before cancer is detected in the exposed group, thus decreasing the magnitude of effect (relative risk), particularly for lower exposure subgroups. Also in cohort studies, the tumor in the exposed group may have started to grow well before or just after exposure took place, increasing the magnitude of effect, particularly for very long latencies. Case-control studies are less sensitive to latency bias because of randomization and matching, but differential effects of latency are expected to be present. A number of biases can be caused in case-control studies when data from cases and controls are collected after too short a period of exposure to EMF (cell phone usage, for instance) and pooled with cases and controls after exposure to longer periods.

A multistage model of cancer causation, such as that proposed by Armitage & Doll (1961), should be used in the design of cancer epidemiological studies. The investigators should lag the observations in relation to exposure, taking into account the known or calculated average time latency for the particular kind of cancer (Gail & Bénichou, 2001), a value that is often unknown or has not been observed.

Epidemiological studies over extended periods of time are difficult to carry out and most of the cell phone users in the world have less than 5 years of usage, so this is not easy to solve. Furthermore, the relevant lag periods for health effects of RF are presently unknown, but should be very long, and hence missed by current studies.

Selection bias is very common in retrospective case-control studies and may operate by either by conscious or unconscious inclusion or participation of subjects. Another selection bias is created by leaving out the data of people who refused to participate or who dropped out of the study, because they may have done this due to some reason that will introduce a systematic error in the sampling. Potential for selection bias has been evaluated in an INTERPHONE study (Vrijheid *et al*, 2009b) by using information from non-response questionnaires (NRQ) completed by a sub-set of non-participants. Regular mobile phone use was reported less frequently by controls (56%) and cases (50%) in the non-participants. than by those who participated (controls, 69%; cases, 66%). The results suggested that *“refusal to participate is related to less prevalent use of mobile phones, and that this could result in a downward bias around 10% in odds ratios for regular mobile phone use”*. In addition, a low response rate, particularly among controls, introduces bias if participation is related to mobile phone use (Cardis *et al*. 2007). This is a likely to be a partial explanation for why many relative risk estimates in the Interphone study are actually below 1.0 (SCENIHR, 2009). Other examples of selection bias are leaving out corporate uses of cell phones, excluding people with certain kinds of ailments, or when they already had died (a common procedure used to avoid the innacuracy of retroactive reporting by relatives and friends) in so-called “questionnaires by proxy”.

Recall bias: For questionnaire-based retrospective studies, this can be an important and

common source of bias, since self-reported use of cell phones is not a reliable measure, particularly for long term use. Timotijevic *et al.* (2008) have examined the factors influencing self-report of mobile phone use, such as response prompting, time reference and others. A correlation study by Parslow *et al.* (2003) indicated that over-reporting is more common than under-reporting (70% more for the number of calls and 180% more for the duration of calls). Most validation studies report overestimate of duration by a factor of 1.4 and underestimation of number of calls by a factor of 0.81 (Vrijheid *et al.* 2008, 2009). Such a high magnitude of error would not be tolerated in any other self-respecting scientific investigation, although in epidemiology the use of randomization, matching and relative risk calculations somehow are able to attenuate bias influence, unless it occur in different ways in the case and control groups or in the different arms of cohort studies.

The INTERPHONE study group went to great lengths to investigate, for the first time, how prevalent and serious is recall bias (Vrijheid *et al.*, 2006a, Samkange-Zeeb *et al.*, 2004). As suspected, they concluded that for 6 months only, *“volunteer subjects recalled their recent phone use with moderate systematic error and substantial random error. This large random error can be expected to reduce the power of the Interphone study to detect an increase in risk of brain, acoustic nerve, and parotid gland tumours with increasing mobile phone use, if one exists.”* and that although reported number of calls correlated rather well with the golden standard provided by telecom records of calls, within a 3 months period, this was not so with reported duration of calls. These results were extended in a publication by the same group in 2009, where it was found that *“for cases, but not controls, ratios increased with increasing time before the interview; however, these trends were based on few subjects with long-term data. Ratios increased by level of use. Random recall errors were large (...) apparent overestimation by cases in more distant time periods could cause positive bias in estimates of disease risk associated with mobile phone use.”*

In another validation study (Berg *et al.*, 2005), emitted power by mobile phones was correlated with user's reports of intensity of usage (number and duration of calls made). The correlation was significant, but low (0.5 and 0.48 for number and duration respectively). Recalls for longer periods were not investigated, but surely they would be even less correlated, The impact of selection and recall biases on epidemiological studies of RF and health was also studied quantitatively by means of simulations by Vrijheid *et al.* (2006b, 2009), who arrived at the same conclusions. Recall bias for estimates of cell phone usage using self-report in a case/control study versus telephone subscriber data submitted by companies in a retrospective cohort study permitted Schütz and Johansen (2008) to compare their reliabilities. The result was a low agreement (0.3), very low sensitivity (30%) and good specificity (94%). Odds ratios calculated for both data sets resulted in a difference of up to 0.2 points.

Differential recall bias: people who have a tumor or health ailment, for example, which they believe or are led to believe by the investigators themselves or mass media, tend to recall with bias. Recall bias might be particularly strong for the side of head (laterality) of phone use, since subjects have a tendency to point to the side of the tumor, when asked about what side they used the handset more.

Reporting bias: two problems may occur in retrospective studies with cases going back many years in the past, especially with fatal diseases such as neoplasias. Firstly, a considerable amount of data about exposure in people who are deceased is based on second-hand reporting by close living relatives. This is called reporting by proxy. Surely

this reduces greatly the accuracy of data and should be avoided, although this is impossible in some cases. It is a dilemma, because maintaining proxy interviewing introduces biases (since proxy reporting is more common in cases than in controls, due to mortality or severity of disease), while its elimination would introduce another kind of bias (better data quality in controls, exclusion of patients who are unavailable at the time of retrospective data collection,). Secondly (and more serious because it is difficult to detect and correct), brain, memory and cognition might be affected by disease, and introduce inaccuracies or false reporting by affected patients (Ahlbom *et al.* 2004).

Non-blinded data collection and reporting biases: In a study conducted in Germany, residents of a neighborhood were actually *communicated* to by the investigators that they were being recruited for evaluating bad health caused by an antenna situated near their homes, a fact that many ignored until then! Methodological, elementary errors such as these are actually very common, as blinding or double-blinding is not always entirely impossible. According to Valberg *et al* (2007), most of these epidemiological studies would be rejected for publication if they should follow the standards of quality demanded of clinical research.

Conclusions regarding methodological problems

In conclusion, there are many methodological difficulties which seem to affect epidemiological studies in this area, particularly of case/control designs. The most common problems to be considered here are:

- Poor estimation of exposure
- Differential action of recall bias
- Selection bias

The most difficult and most important considerations in planning the protocol of a case-control study are ascertainment of cases, selection of controls and the quality of the exposure measurement (Wacholder, 1995). |

What can be done to improve the quality and resolution of epidemiological studies?

First of all, we need better methods as well as better reporting. Groups of concerned epidemiological investigators have dedicated their time to draw up better practice guidelines (e.g., Stroup *et al.*, 2000; Blettner *et al.*, 2001; Pocock *et al.*, 2004). Systematic, transparency are now the aim of most reviews.

According to Auvinen *et al* (2006). *“the major opportunity to improve the quality of evidence is through prospective studies. The major limitation of epidemiological studies addressing the health effects of mobile phone use is related to exposure assessment. These limitations are inherent in case-control studies. Quality of evidence can be improved by conducting prospective cohort studies.”*

SCENIHR, the Scientific Committee on Emerging and Newly Identified Health Risks, a consulting body set up by the European Community has identified as the best way to fill the present research gaps in human epidemiological studies as:

A long-term prospective cohort study is the next logical step in the hierarchy of evidence following inconclusive results of previous case-control studies. A cohort study overcomes shortcomings of case-control studies, such as recall bias and selection

bias, as well as uncertainty due to self-reported retrospective exposure assessment. Such a study would also significantly expand the narrow scope of outcome in previous studies that were mainly limited to intracranial tumours. Additional outcomes include e.g. neurological diseases, cerebrovascular diseases, and other types of cancer. Prospective studies can consider not only the effects of current exposure but also exposure history incurred prior to start of follow-up as well as exposure from new technologies, developed during the course of the study. (SCENIHR, July 2009).

In this respect, a number of prospective cohort studies with long duration (20 to 30 years) are beginning, such as COSMOS (International Cohort Study of MOBILE Phone Use and Health, see Schüz, 2006), carried out by the Department of Epidemiology and Public Health at Imperial College London, UK and a number of other countries (Sweden, Denmark etc. The costs of these kinds of study are large, and its long term funding is usually not entirely assured, but they are certainly necessary to provide final assurance to science and the public of the long-term safety of cell phones.

In relation to children, SCENIHR (2009) also proposed in its report on current research gaps on EMF and health:

Children are exposed to RF fields from mobile telecommunications equipment earlier and thus have longer life-time exposure than present day adults. They may also be more susceptible than adults due to anatomical and morphological differences and as they are exposed during development. Available and ongoing research is mainly limited to case/control studies on childhood brain tumours. Hardly any research has been done on the effects of exposure to EMF on the development of the central nervous system, on cognitive functions in children, and on behaviour. More data are also needed on children younger than those who have been studied to date. Animal experiments on early brain and behaviour development can answer some of the questions related to effects on children.

Elimination of exposure assessment errors will only be achieved by using personal dosimeters that are capable of recording the whole spectrum, and continuous, maintenance-free and reliable recording. This is the single most important technological innovation to change the current scenario, but its deployment with large number of participants is very costly (consider, for example, the comparison with radiodosimetry using photographic film badges for determining ionizing radiation exposure, which tags millions of occupational users every year around the globe, is very cheap, is easily quantifiable and reasonably reliable). In a meeting held in January 2008, titled “*Dosimetry Meets Epidemiology*”, it was confirmed that “*monitoring is a sine qua non to assess the public health situation and a parallel should be drawn in RF research, where the question should focus not only on mechanisms but indeed on public health. In addition, knowledge about the extent of public exposure will be mandatory if consistent evidence of adverse non-thermal effects of ELF and RF exposures may be established eventually*”.

The first studies are beginning to appear along these lines. In Germany, with users carrying a personal dosimeter for 24 hours and measurements every second, Kühnlein *et al.* (2008) determined that the overall exposure to RF fields of all assessed individuals was markedly below the ICNIRP reference level.

Another technical improvement that might render better exposure assessment on a

continuous basis for epidemiological investigations on cell phone users are special handsets which were modified (SMP: Software Modified Phone) to record for every call the output power. Although it still is not a true measurement of SAR, the correlation could be good enough. An investigation using SMPs, comprising more than 60,000 calls, was carried out by Vrijheid *et al* (2009a). They concluded that the average power used was 50% of the maximum, that output power varied by a factor of up to 2 to 3 between study centres and network operators, that in about 39% of the time, conversations were held at maximum power, and that this increased much when they happened in rural locations, due to a larger distance from the base station. They concluded that there appears to be little value in gathering information on circumstances of phone use

A good example of what resolute contributions such kind of epidemiological study can make is the longitudinal, prospective investigation of exposure to tobacco and health outcomes in 34,439 physicians of the UK National Health Service along five decades (Doll *et al*, 2004). The degree of exposure was recorded with reasonable accuracy, without large reporting or recall biases, it was based on a known reliable relationship between exposure (smoke inhaling) and blood concentration of chemicals, risk assessment and recording of health outcomes with long latencies was close to ideal (98.9% of causes of death were identified), large numbers of participants and continuing adherence to the study (94%), and several other such features. Thus, a cause-effect relationship could be firmly established in a field fraught with uncertainties until then, and which changed forever public attitudes toward tobacco (by showing for example, that smokers had a relative risk of 3 dying earlier compared to non-smokers)

If we refer to the Bradford Hill's (1965) "nine points" for assigning a good chance of cause-effect to epidemiological studies, we can easily ascertain that the body of evidence so far does not satisfy them entirely, in regard to RF field exposure and possible effects on human health:

1. **Strength of association** measurements, such as RRs, ORs and SIRs are usually small, close to unity, so they do not point out a significant strength of association;
2. **Intra- and inter-studies consistency**: scientific controversy has been fueled by a notable inconsistency among studies for several health outcomes, reproducibility of positive results is low, and comparison is difficult due to large differences in study quality and methodology;
3. **Specificity of the association**: although specific associations have been sought by epidemiological studies, they are still controversial since many studies contradict each other, and the independent variable (exposure) has been measured with a large margin of inaccuracy and a large number of uncontrolled variables;
4. **Temporality**: most of the studies examined exposure before disease; but since the start of disease is not the same as first detection of disease, particularly in cancers with very long development times, the temporality of cause before disease is somewhat blurred;
5. **Dose-response relationship**: very few studies examined this parameter, in part due to methodological difficulties. In most community-exposure studies, such a relationship, assessed indirectly by distance from the base tower, was either not proved or unreliable data could explain better the slight variations observed. In studies of cell phone usage, the number and duration of calls were commonly used

as a dosing parameter, but recall bias could have influenced its accuracy.

6. The very low levels of RF fields emitted by base stations do not support a **biological, physical and chemical plausibility**. Cell phones on the other hand produce relatively high exposures, so this becomes more plausible, but the majority of published research have not provided a firm basis for such effects even at these higher levels of exposure.
7. **Biological coherence**: Contrariwise to ionizing radiation, RF rarely has biological and molecular counterparts that would explain damage to the cell machinery, and so disease mechanisms at very low levels are unlikely. It is doubtful whether non-thermal effects are a significant phenomenon for promoting disease.
8. There is no **consistent support for positive epidemiological studies from experiments**, either in animals or humans
9. An **analogy to other similar, discovered cause-effect relationships**, such as with ionizing radiation, has not been ascertained so far, and it is several orders of magnitude lower, if it eventually is proved to exist (one main reason being that RF has no cumulative biological effects). One possible analogy might be with extremely low frequency fields, such as are emitted by power lines, and which have been concluded by IARC as a possible carcinogenic agent. Entirely different biophysical mechanisms exist for ELF and RF.